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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,131	08/31/2001	Martin G. Sirois	631020.90015	3085

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/23/2002

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/945,131	SIROIS ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-20 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-20 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-20 are pending in the instant application.

Priority

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

Claim Objections

Claim 17 is objected to because of the following informalities: Claim 17 has a typographical error in that "form" should read "from". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 18 recites the limitation, "polymer" in line 1. There is insufficient antecedent bases for this limitation in the claim. It appears that applicants are intending to recite "copolymer" rather than "polymer".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-8, 10-13 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Sirois et al. (Circulation, 1997 Vol. 95:669-676).

Claims 1-4, 6-8, 10-13 and 20 are drawn to a method of inhibiting restenosis by administering a phosphorothioate antisense oligonucleotide targeted to PDGFR-β transcripts, via catheter, wherein the antisense is in an implantable matrix.

Sirois et al. disclose an EVAc matrix comprising 400 μg of a phosphorothioate modified 18-mer antisense oligonucleotide targeted to PDGFR-β transcripts that was implanted into the rat

aorta via catheter thereby resulting in inhibition of restenosis (see page 670, column 2 and Figures 4-6).

Claims 1-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Rosenberg et al. [WO 93/08845].

Claims 1-4 and 6-20 are drawn to a method of inhibiting restenosis by administering a phosphorothioate or 3' capped antisense oligonucleotide targeted to PDGFR-β transcripts, via catheter, wherein the antisense oligonucleotide is in an implantable matrix such as a hydrogel comprising polyethylene oxide and polypropylene oxide. Claim 5 is drawn to a method of inhibiting restenosis by administering a gene selected from the group consisting of c0myb, NMMHC and PCNA.

Rosenberg et al. disclose methods of inhibiting restenosis comprising administering, via catheter, modified antisense oligonucleotides (at least 14 nucleotides in length and 30 to 3000 μg per square centimeter of tissue surface area), in a hydrogel (which is liquid below body temperature), containing from about 10 to about 80% by weight ethylene oxide and from about 20 to about 90% by weight propylene oxide or about 70% polyethylene oxide and 30% polypropylene oxide, targeted to PDGFR-β transcripts comprising phosphorothioate or 3' cap modifications (see pages 6, 7, 13, 15, 16 and 20). Rosenberg et al. further disclose that antisense oligonucleotides specific for c-myb, NMMHC and/or PCNA may be administered to a patient who is at risk for restenosis due to angioplasty or other procedure (see page 16 and SEQ ID NOs: 1, 2 and 4).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sirois et al. (Circulation, 1997 Vol. 95:669-676) and Rosenberg et al. [WO 93/08845] in further view of Rosenberg et al. [U.S. Patent No. 5,593,974].

Claims 1-20 are drawn to a method of inhibiting restenosis by the administration of a phosphorothioate or 3' capped antisense oligonucleotide targeted to PDGFR-β transcripts and c-myb, NMMHC or PCNA transcripts, via catheter, wherein the antisense oligonucleotide is in an implantable matrix such as a hydrogel comprising polyethylene oxide and polypropylene oxide.

Sirois et al. teach an EVAc matrix comprising 400 μg of a phosphorothioate modified 18-mer antisense oligonucleotide targeted to PDGFR-β transcripts that was implanted into the rat aorta via catheter thereby resulting in inhibition of restenosis (see page 670, column 2 and

Figures 4-6). Sirois et al. further teach that antisense oligonucleotides directed against growth-regulatory or cell cycle genes (c-myb, c-myc, PCNA) involved in vSMC proliferation after injury have successfully altered intimal hyperplasia (see page 669, last paragraph). Sirois et al. do not teach targeting NMMHC, 3' capped oligonucleotides, or a hydrogel comprising polyethylene oxide and polypropylene oxide.

Rosenberg et al. (WO '845) teach methods of inhibiting restenosis comprising administering, via catheter, modified antisense oligonucleotides (at least 14 nucleotides in length and 30 to 3000 μg per square centimeter of tissue surface area), in a hydrogel (which is liquid below body temperature), containing from about 10 to about 80% by weight ethylene oxide and from about 20 to about 90% by weight propylene oxide or about 70% polyethylene oxide and 30% polypropylene oxide, targeted to PDGFR-β transcripts comprising phosphorothioate or 3' cap modifications (see pages 6, 7, 13, 15, 16 and 20). Rosenberg et al. further teach that antisense oligonucleotides specific for c-myb, NMMHC and/or PCNA may be administered to a patient who is at risk for restenosis due to angioplasty or other procedure (see page 16 and SEQ ID NOs: 1, 2 and 4).

Rosenberg et al. ('974) teach the inhibition of restenosis in rat aortas by administering antisense oligonucleotides, including 3' capped oligonucleotides (see column 6), targeted to c-myb, NMMHC and PCNA transcripts (see claim 19), as well as hydrogels comprising polyethylene oxide and polypropylene oxide. Rosenberg et al. further teach that a mixture of antisense oligonucleotides targeting c-myb and NMMHC resulted in inhibition of restenosis in rabbits (see Figure 9). Rosenberg et al. further teach that antisense oligonucleotides, locally delivered to the alveolar/microvascular area, could be directed against the following targets to

intervene in the pathology outlined above, since the cDNA sequences of all of the targets selected are known. Thus, antisense oligonucleotides specific for mRNA transcribed from the genes would inhibit production of PDGF to prevent recruitment of white cells or resultant fibrosis (see column 8, last paragraph).

It would have been obvious to one of ordinary skill in the art to use oligonucleotides targeted to either c-myb, NMMHC, PCNA transcripts, as taught by Rosenberg et al. ('974), in addition to oligonucleotides targeted to PDGFR-β transcripts as taught by Sirois et al., Rosenberg et al. ('974), and Rosenberg et al. (WO '845) since Rosenberg et al. ('974) clearly teaches targeting multiple transcripts inhibits restenosis. One of ordinary skill in the art would have had a reasonable expectation of success in using the antisense oligonucleotides taught by Rosenberg et al. ('974) in the methods of Sirois et al. and Rosenberg et al. (WO '845) since all of the above transcripts are known to be involved in restenosis and would at the least have an additive effect in inhibiting restenosis. Moreover, modifying the phosphorothioate oligonucleotides as taught by Sirois et al. with a 3' cap would have been further obvious since many modifications are known and used in the art to increase nuclease stability without affecting activity of the oligonucleotide as taught by Rosenberg et al. ('974). Furthermore, the use of hydrogels comprising polyethylene oxide and polypropylene oxide polymers is also well known in the art as a means of delivering an oligonucleotide locally as is taught by Rosenberg et al. ('974).

Therefore, the invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rosenberg et al. [U.S. Patent No. 5,593,974] in view of Rosenberg et al. [WO 93/08845] and Koyama et al. (Circulation Research, 1994 Vol. 75:682-691).

Claims 1-20 are drawn to a method of inhibiting restenosis by the administration of a phosphorothioate or 3' capped antisense oligonucleotide targeted to PDGFR-β transcripts and c-myb, NMMHC or PCNA transcripts, via catheter, wherein the antisense oligonucleotide is in an implantable matrix such as a hydrogel comprising polyethylene oxide and polypropylene oxide.

Rosenberg et al. ('974) teach the inhibition of restenosis in rat aortas by administering antisense oligonucleotides, including 3' capped oligonucleotides (see column 6), targeted to c-myb, NMMHC and PCNA transcripts (see claim 19), as well as hydrogels comprising polyethylene oxide and polypropylene oxide. Rosenberg et al. further teach that a mixture of antisense oligonucleotides targeting c-myb and NMMHC resulted in inhibition of restenosis in rabbits (see Figure 9). Rosenberg et al. further teach that antisense oligonucleotides, locally delivered to the alveolar/microvascular area, could be directed against the following targets to intervene in the pathology outlined above, since the cDNA sequences of all of the targets selected are known. Thus, antisense oligonucleotides specific for mRNA transcribed from the genes would inhibit production of PDGF to prevent recruitment of white cells or resultant fibrosis (see column 8, last paragraph).

Rosenberg et al. (WO '845) teach methods of inhibiting restenosis comprising administering, via catheter, modified antisense oligonucleotides (at least 14 nucleotides in length and 30 to 3000 μg per square centimeter of tissue surface area), in a hydrogel (which is liquid below body temperature), containing from about 10 to about 80% by weight ethylene oxide and

from about 20 to about 90% by weight propylene oxide or about 70% polyethylene oxide and 30% polypropylene oxide, targeted to PDGFR-β transcripts comprising phosphorothioate or 3' cap modifications (see pages 6, 7, 13, 15, 16 and 20). Rosenberg et al. further teach that antisense oligonucleotides specific for c-myb, NMMHC and/or PCNA may be administered to a patient who is at risk for restenosis due to angioplasty or other procedure (see page 16 and SEQ ID NOs: 1, 2 and 4).

Koyama et al. teach that PDGFR-β is involved in intimal thickening (e.g. restenosis) and further, that inhibition of PDGFR-β using monoclonal antibodies resulted in inhibition of vascular smooth cell migration, which is a process resulting in intimal thickening.

It would have been obvious to one of ordinary skill in the art to use an antisense composition comprising oligonucleotides targeted to either c-myb, NMMHC or PCNA transcripts as taught by Rosenberg et al. ('974) in addition to PDGFR-β as taught be Rosenberg et al. (WO '845) and Rosenberg et al. ('974) since all of said transcripts are involved in restenosis as taught by Rosenberg et al. ('974) and Koyama et al. and would have at least resulted in an additive effect. Moreover, Rosenberg et al. ('974) clearly provide motivation to target multiple transcripts using antisense oligonucleotides as is evidences by Rosenberg et al. ('974) rabbit model discussed above.

Therefore, the invention would have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
October 17, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635